

03-C-0032: Intrathecal Gemcitabine Therapy for Neoplastic Meningitis: A Phase I and Pharmacokinetic Study

This protocol is coordinated by Texas Children's Hospital. The trial is designed to study the incidence and severity of toxicity from the intrathecal injection of gemcitabine in patients with meningeal cancers that are refractory to conventional therapy; and to identify a safe dose of gemcitabine that can be recommended for intrathecal administration in subsequent phase II trials. The CSF pharmacokinetics of intrathecal gemcitabine will also be studied. The starting dose is 5 mg, with planned escalations to 10, 20, 30, 40 and 50 mg. In the first patient cohort, gemcitabine will be administered intrathecally on a weekly schedule for a six week induction, and subsequent cohorts will be treated twice weekly during induction. The induction is followed by weekly x 6 weeks consolidation, twice monthly x 4 months and then monthly.

ELIGIBILITY CRITERIA:

Age: Patients must be ≥ 3 years of age

Diagnosis: Patients must have neoplastic meningitis secondary to an underlying leukemia/lymphoma or a solid tumor (including primary CNS tumors or carcinomas of unknown primary site) for which there is no conventional therapy. Patients with CNS leukemia/lymphoma must be refractory to conventional therapy, including XRT (i.e. 2nd or greater relapse). *Neoplastic meningitis is defined as follows:*

- Leukemia/Lymphoma: CSF cell count $> 5/\mu\text{L}$ AND evidence of blast cells on cytospin preparation or by cytology.
- Solid tumor: Presence of tumor cells on cytospin or cytology OR presence of meningeal disease on MRI scans.

Life Expectancy: of at least 6 weeks

Performance Status: Patients > 10 years old should have Karnofsky performance status of $\geq 50\%$ and patients ≤ 10 years old should have a Lansky performance status of $\geq 50\%$. Patients who are unable to walk because of paralysis, but who are in a wheelchair, will be considered ambulatory for the purposes of the performance score.

Recovery from Prior Therapy:

- Patients must have recovered from the acute neurotoxic effects of all prior chemotherapy, immunotherapy, or radiotherapy prior to entering this study.
- Patients must be without uncontrolled significant systemic illness (e.g. infection, except HIV).
- Patients must not have received any systemic CNS-directed therapy within 3 weeks or craniospinal irradiation within 8 weeks prior to starting treatment on this study.
- Patients must not have received any intrathecal therapy within 1 week prior to starting treatment on this study.

Hematologic Status: Patients must have a platelet count $> 40,000/\text{mm}^3$ and Hct $> 30\%$. Transfusions are allowed to achieve these values within 48 hours prior to intrathecal gemcitabine treatment. Patients must also have an ANC of $> 1000/\mu\text{L}$.

Hepatic Function: Patients must have adequate liver function, total bilirubin $< 2.0 \text{ mg\%}$, SGPT $< 5 \text{ ULN}$

Renal Function: Patients must have adequate liver function, total bilirubin $< 2.0 \text{ mg\%}$, SGPT < 5 times upper limits of normal; adequate renal function (serum creatinine < 2 times upper limits of normal for age).

<u>Age</u> (years)	<u>Maximum Serum Creatinine</u>
≤ 5	0.8 mg/dl
5 < age ≤ 10	1.0 mg/dl
10 < age ≤ 15	1.2 mg/dl
> 15	1.5 mg/dl

Informed Consent: All patients or their legal guardians (if the patient is < 18 years of age) must sign a document of informed consent according to their institutional guidelines. When patients < 18 years of age will be involved in all discussions in order to obtain verbal assent.

Durable Power of Attorney (DPA): All patients ≥ 18 years of age must be offered a DPA.

EXCLUSION CRITERIA:

Concomitant Therapy:

- Patients receiving other therapy (either intrathecal or systemic) designed to treat their leptomeningeal disease are not eligible for this study. However, patients receiving concomitant chemotherapy to control systemic disease or bulk CNS disease will be eligible, provided that the systemic chemotherapy is not a phase I agent, an agent that significantly penetrates the CSF [e.g. high-dose methotrexate (> 1 g/m²), thiotepa, high-dose cytarabine (> 1 g/m²), 5-fluorouracil, intravenous 6-mercaptopurine, nitrosoureas, temozolomide, or topotecan], or an agent known to have serious unpredictable CNS side effects. Careful documentation of concurrently administered systemic drugs is required. (Please discuss plans for systemic therapy with the Study Chair or Principal Investigator prior to study entry).
- Nuclear medicine CSF flow studies are required within the 2 weeks prior to study entry for all solid tumor patients. In leukemia/lymphoma patients a CSF flow study is only required if CSF analysis or an MRI suggests that there is a blockage to CSF flow. Patients with clinical evidence of obstructive hydrocephalus are not eligible for this protocol. Nor are patients with compartmentalization of CSF flow as documented by radioisotope Indium¹¹¹ or Technetium⁹⁹-DTPA flow eligible for this protocol. If a CSF flow block or compartmentalization is demonstrated, focal radiotherapy to the site of the block to restore flow followed by a repeat CSF flow study demonstrating clearing of the blockage is required for the patient to be eligible for the study.
- Patients with clinically significant abnormalities of serum electrolytes, Ca⁺⁺, Mg⁺⁺ and Phosphorus are excluded.
- Patients with a ventriculoperitoneal (VP) or ventriculoatrial (VA) shunt are not eligible unless they are shunt-independent and there is evidence that their shunt is nonfunctional (e.g. CSF flow study demonstrating normal flow).
- Patients who have leukemia/lymphoma with a concomitant bone marrow relapse are not eligible for this study.
- Women of childbearing age must not be pregnant or lactating. (Male and female patients who are fertile must be willing to use an effective means of birth control to avoid pregnancy.)
- Patients must be free of uncontrolled infection except HIV (i.e., AIDS-related lymphomatous meningitis).

- Patients must NOT be receiving any other investigational agents and must not have received any other investigational agent within 14 days prior to study treatment. The 14 day period should be extended if the investigational agent is known to have delayed toxicity.
- Patients with impending spinal cord compression, CNS involvement or requiring local XRT (e.g. optic nerve), are not eligible for this study.
- Concomitant CNS radiation therapy is not permitted. (Patients are not permitted to receive radiation to any port that encompasses any part of the brain or spine while on study.) Patients may receive radiation therapy to extra-CNS sites, e.g. painful bone metastases not in the craniospinal axis.

PRETREATMENT EVALUATION:

Unless otherwise specified, prestudy exams must be performed within 72 hours prior to entry on study.

- Complete history and physical examination, including a detailed neurological examination.
- CSF access devices (e.g. Ommaya reservoir or lumbar access devices) are optional. Drug may be administered by intralumbar injection (lumbar puncture or intralumbar access device) or through a ventricular access device.
- Required CSF Studies
- **For patients with leukemia/lymphoma:**
 - Lumbar puncture must be performed within 72 hours of study entry or at the time the first dose of study drug is administered, to document the existence and extent of meningeal disease. CSF cytospin, cell count, differential, protein, and glucose are required.
 - For patients with an Ommaya Reservoir, taps must be performed within 72 hours of study entry or at the time the first dose of study drug is administered, to document the existence and extent of meningeal disease. CSF cytospin, cell count, differential, protein, and glucose are required.
- **For Patients with leptomeningeal metastasis from solid tumors:**
 - Lumbar puncture must be performed within 7 days of study entry or at the time the first dose of study drug is administered to document the existence and extent of meningeal disease. CSF cytology, cell count, differential, protein, and glucose are required.
 - For patients with an Ommaya Reservoir, taps must be performed within 7 days of study entry or with the first dose of study drug, to document the existence and extent of meningeal disease. CSF cytology, cell count, differential, protein, and glucose are required.
- CSF obtained immediately prior to the first dose of gemcitabine will be used for assessment of response.
- Blood tests including CBC with diff and plt and chemistries (BUN , Cr, SGPT, electrolytes, Ca⁺⁺, Mg⁺⁺, phosphorus, total bili)
- Urine pregnancy test when appropriate
- Bone marrow aspirate (Within 2 weeks prior to study entry) is required for all patients with leukemia/lymphoma and as clinically indicated for solid tumor patients.
- Radiographic studies: (Within 2 weeks prior to study entry and following last dose of intrathecal chemotherapy)
- Solid tumor: MRI of the head and spine, with and without contrast.

- Leukemia/Lymphoma: Head MRI, with & without contrast. Spine MRI with & without contrast, if clinically indicated.
- Nuclear Medicine studies: (Within 2 weeks prior to study entry)
- Solid tumor: Indium¹¹¹-DTPA or Technetium⁹⁹-DTPA CSF flow study is required.
- Leukemia/Lymphoma: Pre-treatment radionuclide CSF flow study is required if CSF analysis or MRI scan suggests a CSF blockage.

GENERAL TREATMENT PLAN: The starting dose is 5 mg, with planned escalations to 10, 20, 30, 40 and 50 mg. In the first patient cohort, gemcitabine will be administered intrathecally on a weekly schedule for a six week induction, and subsequent cohorts will be treated twice weekly during induction. The induction is followed by consolidation (weekly x 6, then twice monthly x 4 months and then monthly for up to 1 year).

PHARMACOKINETIC STUDIES: Will be performed only in patients with ommaya reservoirs during their first course of therapy. Ventricular CSF (0.5 cc) should be obtained at prior to drug administration, at 5, 15, 30 and, 45 minutes, 1, 2, 3, 6-8, and 24 hrs following intraventricular drug administration. Blood (3 ml/sample) will be drawn at the same times. When possible, a lumbar CSF sample should be obtained at 2 hr following intraventricular drug administration.

HOSPITALIZATION: Overnight hospitalization for observation after the initial dose of gemcitabine is required.

ACCRUAL: Open to accrual. Patients meeting the eligibility criteria can be referred to the Pediatric Oncology Branch, NCI for evaluation and treatment. Other participating institutions include the Texas Children's Hospital, University of Pittsburgh Cancer Institute, Children's Hospital of Pittsburgh, and Seattle Children's Hospital.